UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/578,521 | 05/08/2006 | Jong-Yoon Chun | 50413/015001 | 7873 |

21559 7590 12/01/2010

CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

| EXAMINER | |
|---|---|
| PANDE, SUCHIRA | |
| ART UNIT | PAPER NUMBER |
| 1637 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 12/01/2010 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/578,521 | CHUN, JONG-YOON | |
| | Examiner | Art Unit | |
| | SUCHIRA PANDE | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-5 and 7-29* is/are pending in the application.

4a) Of the above claim(s) *8,12,17,21 and 23-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,9-11,13-16,18-20 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/27/2010 has been entered.

### *Election/Restrictions*

2. Applicant's election without traverse of Group I invention claims 1-25 and 30 in the reply filed on June 19, 2008 was acknowledged in the office action mailed on 10/1 2008. Applicant had also elected species (i) primer of formula I. Non elected claims drawn to product and non elected primer species (primer of formula I and II) were withdrawn from consideration. Consequently claims 1-7, 9-11 and 13-22 and 30 were examined.

Since the instant application is request for continued examination (RCE), of the previously examined invention, claims drawn to product or non elected species of primers previously withdrawn properly remain withdrawn. Amended base claim does not recite primer of formula II and III, hence Examiner will not examine withdrawn claims drawn to non elected species of primers.

### *Claim Status*

3. Claims 6 and 30 are cancelled; claims 8, 12, 17, 23-29 drawn to non elected invention remain withdrawn. Claims 1 and 21 have been amended; Amendment to claim 21 makes it dependent on withdrawn claim 8, hence claim 21 is withdrawn from consideration. Currently claims 1-5, 7, 9, 13-16, 18-20 and 22 are active and will be examined to the extent they read upon the elected species of primer of Formula I in this action.

***Claim Interpretation***

4. The claims currently under consideration are method claims for amplifying nucleic acids. The claims recite structural limitations of the primers used in the method. No specific template nucleic acid is recited in the claims. In view of this scenario, the limitations wherein specific portions of said primers are substantially complementary to, a template nucleic acid, therefore reads on a method where the claims encompass primers for any conceivable nucleic acid template, whether naturally occurring or man-made, whether known to exist or capable of being synthesized. Any conceivable nucleic acid sequence can be synthesized and engineered in such a way as to produce gDNA, cDNA or mRNA. In this regard, those particular limitations of the claims pertaining to substantial complementarity are met by any primer depending on the template nucleic acid. Since no specific template is recited in the claims, limitations based on hybridization to random or arbitrary sequence with respect to an unspecified template impart no structural limitation on the claimed primers that are useful in the method, therefore any primer will function in the claimed method.

Although the references upon which the 35 U.S.C. 102 rejections below are based may disclose a "template" or "target" for the primers taught, such templates or targets are not limiting in the application of the disclosed primers as prior art against the claims because the prior art primers could be used with other targets or templates. DNA Walking annealing control primer (DW-ACP) has not been defined, so using broadest reasonable interpretation any primer used in prior art will read upon claim 1 as currently recited.

***Response to Arguments***

Re 103 rejection of claims 1-5, 7, 13-16 and 18-22 over Stone & Wharton as evidenced by Welsh & McClelland (1990) in view of Brenner further in view of Chun

5. Applicant's arguments filed 1/27/2010 have been fully considered but they are not persuasive. Applicant has amended base claim 1 to add limitation "the annealing portion of the first DW-ACP is restricted to the portion consisting of said degenerate random nucleotide sequence and hybridizing nucleotide sequence at the first annealing temperature."--.

---- "r represents an integer from 2 to 5, and Yq is continuously followed by Zr.

The addition of these limitations changes the scope of the claimed invention. Hence previously cited rejection is not valid and is being withdrawn.

Chun (previously cited) teaches the changed scope of the invention.
In the rejection that follows Examiner will describe how Chun teaches the invention instantly recited.

Re 103 rejection of claims 9-11 over Stone & Wharton as evidenced by Welsh & McClelland ; Brenner in view of Chun as applied to claim 1 above and further in view of Liu & Whittier ; Watanabe et al. and Oberste et al.

6. Since rejection of claim 1 over Stone & Wharton as evidenced by Welsh & McClelland; Brenner in view of Chun is withdrawn, hence rejection of claims 9-11 further in view of secondary art is also withdrawn.

***Claim Rejections - 35 USC § 112***

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 1 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 step (a-2-3) has been amended to add limitation------ "and Yq is continuously followed by Zr."

Examiner has searched the specification as filed and did not come across any place where limitation---- "Yq is continuously followed by Zr" is specified. This is a NEW MATTER rejection.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 1 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

claim 1 is indefinite for the following reasons.

- step (a-1) recites that the "annealing portion of the first DW-ACP is restricted to the portion ***consisting of said degenerate random nucleotide sequence***" but formula 5'-Xp-Yq-Zr-Qs-3' is recited has having a Zr which represents a degenerate random sequence portion having a degenerate random nucleotide sequence which is separate from Qs which "represents a 3' end portion having a hybridizing nucleotide sequence substantially complementary to a site on said unknown nucleotide sequence." Since DW-ACP must anneal and extend for amplification to occur, the Qs portion must also hybridize. However, the new amendment prevents the 3' end (or Qs) to hybridize to the unknown sequence as it was amended to recite that the annealing portion of DW-ACP is "restricted to" only the degenerate random nucleotide sequence which is Zr.

- Second point is that while r is explicitly limited to the integers of 2 to 5, none of the other integers (p, q, or s) are recited as having any integers. This means that they need not be there (p=0, q=0 and s=0), which results in the DW-ACP primer being a random hexamer or anything else. If this is indeed the case then, art reading on random hexamer or anything else will apply in addition to the cited art.

***Claim Objections***

11. Claim 7 objected to as being dependent upon a rejected base claim 1 but it falls outside the scope of the claim 1 from which it depends.

Claim 7 recites that the regulator portion in the first degenerate DW-ACP is capable of restricting the annealing portion of the primer to its 3' end portion at said first annealing temperature. Claim 1 limits all of the claimed embodiment to the DW-ACP primer only annealing to the degenerate portion of the primer (Zr) and therefore the 3' end (Qs) should and cannot hybridize (anneal) to the target. This is 112, 4th para objection.

12. Withdrawn Claim 8 objected to because of the following informalities: claim 8 depends from a canceled claim. Appropriate correction is required.

13. Claim 22 objected to under 37 CFR 1.75(c) as being in improper form because claim 22 is a multiple dependent claim that refers to limitation which may not be found in its parent claim. For example, claim 22 can depend from claim 1 and recite, wherein "s or w represents." When dependent from claim 1, there is no antecedent basis for "w."

***Claim Rejections - 35 USC § 102***

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1-5, 7, 13-16 and 18-20, 22 are rejected over Chun (WO 03/050305 A1 published on 19 June 2003 with filing date of 19 September 2002 previously cited).

Regarding claim 1, Chun teaches use of ACP (see title where Annealing control primer ACP is taught).

Chun also teaches primer where DW-ACP has a general formula I:

5'-$X_p$-$Y_q$- $Z_r$-$Q_s$-3' (I) (See page 101 lines 26 to 27 where primer identified by SEQ ID NO: 75 is taught).

wherein, $X_p$ represents a 5'-end portion having a pre-selected nucleotide sequence, (The sequence GTCTACCAGGCATTCGCTTCAT at 5'end of this primer = $X_p$ represents a 5'-end portion having a pre-selected nucleotide sequence),

$Y_q$ represents a regulator portion comprising at least two contiguous universal base or non- discriminatory base analog residues (string of 5 inosines IIIII following the sequence $X_p$ = $Y_q$ represents a regulator portion comprising at least two contiguous universal base or non- discriminatory base analog residues),

$Z_r$ represents a degenerate random sequence portion having a degenerated random nucleotide sequence (the five nucleotides TTGCA following the string of inosines = $Z_r$ represents a degenerate random sequence portion (any of the 4 nts (ATGC) can be in any of these degenerate positions so in the instant case the nts used are TTGCA) having a degenerated random nucleotide sequence. Here r represents an integer from 2 to 5),

Also see primers on bottom of page 104 and top of page105 that are taught as ACP primers comprising degenerate sequences for homeobox sequence at their 3' end portion for the first stage PCR

JYC2-HDI where sequence GTNCRRGTGTG following 5 inosines = $Z_r$ represents a degenerate random sequence portion;

JYC2-HD2 where sequence GTNCRRGTCTG following 5 inosines = $Z_r$ represents a degenerate random sequence portion;

JYC2-HD3 where sequence GTNCRRGTTTG following 5 inosines = $Z_r$ represents a degenerate random sequence portion;

In all these cases and $Y_q$ is continuously followed by $Z_r$

$Q_s$ represents a 3'-end portion having a hybridizing nucleotide sequence substantially complementary to a site on said unknown nucleotide sequence to hybridize therewith (the sequence GTT at 3' end = $Q_s$ for primers JYC1-HD2, JYC2-HD3, JYC2-HD3 : represents a 3'-end portion having a hybridizing nucleotide sequence substantially complementary to a site on said unknown nucleotide sequence to hybridize therewith),

p, q, r, and s represent the number of nucleotides, and X, Y, Z, and Q are deoxyribonucleotide or ribonucleotide.

Regarding claim 1, Chun teaches a method for amplifying an unknown nucleotide sequence adjacent to a known nucleotide sequence, which comprises the step of (a) performing a primary amplification of said unknown nucleotide sequence using a DNA

walking annealing control primer (DW-ACP) and a first target-specific primer; in which said step (a) comprises:

(see Chun page 102 line 22 where Protocol A: two step PCR is taught.):

(a-I) performing a first-stage amplification (see page 102 line 23 where a first-stage PCR amplification is taught) of said unknown nucleotide sequence

at a first annealing temperature (see page 103 line 1 where $60^0$C is taught as a first annealing temperature) ,

comprising at least one cycle of primer annealing, primer extending and denaturing using a first degenerate DW-ACP containing a degenerate random nucleotide sequence to hybridize with said unknown nucleotide sequence and a hybridizing nucleotide sequence substantially complementary to a site on said unknown nucleotide sequence, wherein said first annealing temperature enables said first degenerate DW-ACP to function as a primer, (see page 102 section first stage PCR)

the annealing portion of the first DW-ACP is restricted to the portion consisting of said degenerate random nucleotide sequence and hybridizing nucleotide sequence at the first annealing temperature, whereby a first degenerate DW-ACP extension product is generated (See Chun page 144, claims 78 and 79 where 3' end portion of the primer is taught to be involved in annealing at first annealing temperature and the regulator portion of the primer is taught to be capable of restricting the annealing portion of the primer to the 3' –end portion at first annealing temperature. Since the primer of formula I has a regulator portion this primer necessarily meets the limitation the annealing portion of the first DW-ACP is restricted to the portion consisting of said degenerate

random nucleotide sequence and hybridizing nucleotide sequence at the first annealing temperature ); and

(a-2) performing a second-stage amplification at a second annealing temperature (see page 103 lines 3-10 where a second-stage amplification at a second annealing temperature (higher annealing temperature of $68^0$C is taught as second annealing temperature) to render said first degenerate DW-ACP not to function as a primer (when temperature is increased then due to presence of the regulator region containing Inosines, the first degenerate DW-ACP does not hybridize at higher annealing temperature this thereby first degenerate DW-ACP does not function as a primer), comprising:

(a-2-1) amplifying said first degenerate DW-ACP extension product using said first target-specific primer (primer JYC3 and JYC4 are first target-specific primer see page 103 line 7) to hybridize with a target-specific nucleotide sequence substantially complementary to a site on said known nucleotide sequence, whereby a target-specific primer extension product is generated (also see Fig. 7B where 5' target sequence primer is taught as first target-specific primer) ,

(a-2-2) amplifying said target-specific primer extension product using a second DW- ACP to hybridize with a nucleotide sequence complementary to said first degenerate DW-ACP sequence of said target-specific primer extension product, whereby a second DW-ACP extension product is generated, and

(a-2-3) amplifying said second DW-ACP extension product using said second DW- ACP and said first target-specific primer, whereby a primary amplification product without a degenerate random nucleotide sequence is generated.

(see fig. 7 B where the scheme of amplification in two step PCR is shown (steps recited in a-2-1, a-2-2 and a-2-3) that results in amplification of the target sequence namely (Allele specific PCR). By teaching allele specific PCR, Chun teaches a primary amplification product without a degenerate random nucleotide sequence is generated)

Regarding claim 2, Chun teaches wherein said first-stage amplification is performed for one cycle (see page 102 line 24 where first stage PCR is taught to be conducted by two cycles, thus teaching wherein said first-stage amplification is performed for one cycle).

Regarding claim 3, Chun teaches wherein said second-stage amplification is performed for at least 5 cycles (see page 103 line 9 where second stage PCR is performed for 40 cycles, thus teaching wherein said second-stage amplification is performed for at least 5 cycles).

Regarding claim 4, Chun teaches wherein said first annealing temperature is between about 35°C and 50°C (see page 105, line 17 where first annealing temperature is taught to be 52°C. By teaching first annealing temperature of 52°C, Chun teaches wherein said first annealing temperature is between about 35°C and 50°C).

Regarding claim 5, Chun teaches wherein said second annealing temperature is between about 50°C and 72°C (see page 105, line 17 where second annealing

temperature of 65°C is taught, thus teaching second annealing temperature is between about 50°C and 72°C).

Regarding claim 7, Chun teaches wherein said regulator portion in said first degenerate DW-ACP is capable of restricting the annealing portion of said primer to its 3'-end portion at said first annealing temperature (See page 144, claim 79).

Regarding claim 13, Chun teaches wherein said nucleotide sequence to be amplified is gDNA or cDNA (see page 24 lines 14-16).

Regarding claims 14-16, Chun teaches wherein said universal base or non-discriminatory base analog residue is deoxyinosine (see page 19 line 21, also see page 20, line 21).

Regarding claims 18, Chun teaches wherein p represents an integer of 10 to 60 (See page 101 lines 26 to 27 where primer identified by SEQ ID NO: 75 is taught here . $X_p$ represents a 5'-end portion having a pre-selected nucleotide sequence is shown as sequence GTCTACCAGGCATTCGCTTCAT. So p here is 22).

Regarding claims 19-20, Chun teaches wherein q is at least 3 (claim 19) or wherein q represents an integer of 2 to 10 (claim 20) (see page 20 lines 6-8 where at least 3 universal bases as well as primer containing 2-15 universal bases is taught).

Regarding claim 22, Chun teaches wherein s represents an integer of 3 to 10 (see page104 line 30 where SEQ ID NO 83 is taught. In this JYC2-HD1 primer the sequence at 3' end following NCRR is 8 nt long shown as --GTGTGGTT-3'. Thus teaching wherein s represents an integer of 3 to 10).

16. Claims 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chun as applied to claim 1 above, and further in view of Liu and Whittier (1995) Genomics 25, 674-681 (previously cited); Watanabe et al. 2001 Journal of Microbiological methods 44 : pp 253-262 (previously cited); and Oberste et al. J Clin. Microbiol. Vol. 37 no 5 May 1999 pp. 1288-1293 (previously cited).

Regarding claim 9, Chun teaches method of claim 1 above. But Chun does not teach wherein said method further comprises the step of (c) performing a secondary amplification at a third annealing temperature, comprising at least one cycle of primer annealing, primer extending and denaturing, using a third DW-ACP comprising at its 3'-end portion a nucleotide sequence to hybridize with the opposite-sense nucleotide sequence to said second DW-ACP sequence present at the 3'-end of said primary amplification product and said first target-specific primer of the step (a) or a nested target- specific primer designed to amplify an internal region of said primary amplification product.

Regarding claim 9, Liu and Whittier teaches wherein said method further comprises the step of (c) performing a secondary amplification at a third annealing temperature, comprising a nested target-specific primer designed to amplify an internal region of said primary amplification product. (see page 676 fig. 1 where internal primers SP2 and SP3 are taught for nested PCR referred to as secondary and tertiary PCR in bottom of fig. 1. Thus teaching a nested target-specific primer designed to amplify an internal region of said primary amplification product).

Regarding claim 10, Liu and Whittier teaches annealing temperature is between about 50°C and 72°C (see page 680 par. 2 where guidelines are provided as to how to set annealing temperatures for high stringency conditions. They teach tm's of the specific primers should be at least $10^0$C higher than the average tm's of the AD primers, and the annealing temperatures in the high–stringency cycles should be set as high as possible (usually 1-$5^0$C higher than the calculated specific primers). In the instant case the tm of the AD3 and AD4 primers is 47-$48^0$C see page 675 par. 3 . So using the guidelines the tm of the specific primers SP2 and SP3 used for nested PCR in this case has to be 57-$58^0$C. So the third temperature condition for performing high stringency annealing temperature for nested PCR should be at least 1-$5^0$C higher than the calculated specific primers tm which will be 58-$63^0$C. Thus by teaching annealing temperature of 58-$63^0$C, Liu and Whittier teaches annealing temperature is between about 50°C and 72°C).

Regarding claim 11, Liu and Whittier teaches performing nested PCR where a small aliquot of the amplified product is diluted and used as a template for nested PCR (see page 675 last part of par. 2 in per procedure where secondary and tertiary (nested PCR) PCRs are taught. It would have been prima facie obvious to one of ordinary skill in the art wherein said method further comprises the step (b) of purifying a reaction resultant of the step (a) to remove said first degenerate DW-ACP, said second DW-ACP and said first target-specific primer prior to performing the step (c). One of ordinary skill in the art performs nested PCR to quantify or for un ambiguous detection of the amplified region. Hence the purpose of performing the nested PCR in step C is to obtain

specific amplified product with a reasonable yield for further use. During classic nested PCR simply a dilution of the amplified product is done and to this diluted sample, PCR primers needed for nested PCR are added. That means the mixture on which nested PCR is being performed may still contains some of the original template and degenerate primer/first specific target primers. Therefore by performing the purification of the amplified product all primers used in the previous amplification are removed. Thus this purified product can be used as a template for nested PCR with no possibility of interference from the previously used PCR primers. Purification of PCR product prior to performing nested PCR will ensure that only the PCR product that was amplified initially using degenerate primer and target specific primer is amplified further. There will be no carry over of the primers used initially that can generate spurious background or amplification of some other regions primed by annealing of the degenerate primers on the original template that will still be present if only a dilution was performed as is routine in nested PCRs.

It would have been prima facie obvious to one of ordinary skill in the art to practice the method of Liu and Whittier in the method of Chun at the time the invention was made. The motivation to do so is provided by both Watanabe et al. and Oberste et al.

Chun teaches a method for amplifying an unknown nucleotide sequence adjacent to a known nucleotide sequence. Chun does not teach use of nested PCR.

Liu and Whittier teach two primers that contain universal or non-discriminatory bases in the regulator portion of the arbitrary primers. Motivation to use the inosine

containing arbitrary primers of Liu and Whittier to perform nested PCR in the method of Chun is provided to one of ordinary skill in the art at the time the invention was made by state of the art at that time. A survey of the literature published tells one of ordinary skill that artisans have successfully introduced inosines in the universal primers used for amplifying 16S ribosomal DNA from a community of bacteria. These inosine containing degenerate primers were able to reduce amplification biases caused by mismatches that were observed using unmodified universal primers. (see abstract Watanabe et al. 2001).

Oberste et al. 1999 designed primers to amplify unknown Enteroviruses (EVs). These primers were designed with inosines to account for the differences between different virus groups and for codon degeneracy (the inosine containing primers are shown in Table 1 page 1289 of Oberste et al. 1999). Using this set of inosine containing degenerate primers they were able to amplify 51 EV strains isolated from clinical material between 1991 and 1998. Art taught that there is high degree of genetic diversity among the EVs and therefore posed a challenge in the systematic design of nucleic acid based diagnostic reagents (see page 1292 par. 2 of discussion). Oberste et al. go on to state "Degenerate inosine containing PCR primers were developed to overcome such nucleotide sequence diversity by specifically targeting regions of conserved amino acid sequences". (see page 1292 last part of par. 2 under discussion). Therefore inosine containing primers have been successfully used by one of ordinary skill in the art.

These teachings of Watanabe et al.; and Oberste et al. teach one of ordinary skill that by using the degenerate primers containing inosines taught by Liu and Whittier in the method of Chun they have a reasonable expectation of success in being able to successfully amplify the desired target region from diverse unknown bacterial or viral clinical isolates but also accurately determine the nucleic acid sequence of the identified organism.

***Conclusion***

17. All claims under consideration 1-5, 7, 9, 13-16, 18-20 and 22 are rejected.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUCHIRA PANDE whose telephone number is (571)272-9052. The examiner can normally be reached on 6:30 am -3:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Suchira Pande
Examiner
Art Unit 1637

/Suchira Pande/
Examiner, Art Unit 1637